

Anti-inflammatory phytochemicals for the treatment of diabetes and its complications: Lessons learned and future promise

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ABSTRACT

Diabetes mellitus (type 1 and type 2) and its various complications continue to place a huge burden on global medical resources, despite the availability of numerous drugs that successfully lower blood glucose levels. The major challenging issue in diabetes management is the prevention of various complications that remain the leading cause of diabetes-related mortality. Moreover, the limited long-term durability of monotherapy and undesirable side effects of currently used anti-diabetic drugs underlie the urgent need for novel therapeutic approaches. Phytochemicals represent a rich source of plant-derived molecules that are of pivotal importance to the identification of compounds with therapeutic potential. In this review, we aim to discuss recent advances in the identification of a large array of phytochemicals with immense potential in the management of diabetes and its complications. Given that metabolic inflammation has been established as a key pathophysiological event that drives the progression of diabetes, we focus on the protective effects of representative phytochemicals in metabolic inflammation. This paper also discusses the potential of phytochemicals in the development of new drugs that target the inflammation in the management of diabetes and its complications.

1. Introduction

Diabetes mellitus (DM) is emerging as one of the major burdens on global health and economies with a prevalence that has increased to 8.8 % in adults (20–79 years) [1]. A global increase of 50 % is predicted. Diabetes mellitus (all forms) ranks ninth among the top major causes of morbidity with a serious impact on life expectancy [2]. Although the precise classification of diabetes remains controversial due to the complex nature of its pathogenesis, three major subtypes are universally

acknowledged: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes (GDM) [3]. Along with the increasing impact of genetic disorders, chemical toxicity, sedentary lifestyle and ageing, the modern epidemic of T2DM has shown a marked global escalation, accounting for approximately 90 % of diabetes cases [4]. Moreover, a host of microvascular and macrovascular associated complications further contribute to its mortality and global economic burden. Although multiple factors

are functionally involved in the development of diabetes and its complications, innate immunity has

been considered a crucial driving force in its pathophysiology [5]. Specifically, autoimmunity plays a key role in evoking an inflammatory response in pancreatic islet cells, resulting in β -cell failure in T1DM. Similarly, systemic low-grade inflammation functions as a common mediator during the initiation of T2DM and its progression to micro/macro-vascular complications [6]. A growing body of evidence from clinical studies demonstrates the notable benefits of inflammation-targeted therapies in hyperglycemia, β -cell dysfunction, and insulin resistance in T2DM [7,8].

Phytochemicals are compounds that give plants their color, flavor, and smell. These compounds are thought to be largely responsible for the medicinal properties and health benefits of medicinal herbs. Phytochemicals nonetheless also include poisonous and toxic chemicals.

Despite the explosive research interest in the development of novel chemicals to treat diabetes, its prevalence and associated complications remain

Abbreviations: AMPK, AMP-activated protein kinase; BCAAs, branched-chain amino acids; COX-2, cyclooxygenase-2; CCL5, chemokine (C-C motif) ligand 5; DM, diabetes mellitus; DKD, diabetic kidney disease; DR, diabetic retinopathy; DPN, diabetic peripheral neuropathy; ERK, extracellular signal-regulated kinase; GDM, gestational diabetes mellitus; HepG2, human hepatocellular liver carcinoma cells; iNOS, inducible nitric oxide synthase; IL, interleukin; ICAM-1, intercellular adhesion molecule-1; JNK, c-Jun N-terminal kinase; MAPKs, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein-1; NF- κ B, nuclear factor- κ B; NAFLD, non-alcoholic fatty liver disease; NLRP3, NACHT, LRR and PYD domains-containing protein 3; NRF2, nuclear factor E2-related factor 2; PTP-1B, protein tyrosine phosphatase 1B; PPAR- γ , peroxisome proliferator-activated receptor gamma; ROS, reactive oxygen species; STZ, streptozotocin; SIRT1, sirtuin 1; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TNF- α , tumor necrosis factor; TGF- β 1, transformed growth factor beta-1; TLR4, toll-like receptor 4; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

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extremely high, highlighting the unmet and urgent need for novel candidate chemicals with sufficient effectiveness. Currently, herb-derived phytochemicals are emerging as promising drug candidates in the prevention and treatment of various metabolic disorders, particularly hyperglycemia and dyslipidemia [9–11]. These natural compounds are classified according to their chemical structure (Table 1). Phytochemicals (herbal medicine and their bioactive compounds), which have significant hypoglycemic effects and play a role in prevention of diabetes-related vascular complications, are associated with less toxicity and fewer side effects [12,13]. This paper will focus on the anti-inflammatory effects of phytochemicals in the prevention and treatment of diabetes and its complications.

This review primarily aims to discuss recent advances in the mechanistic link between metabolic inflammation and diabetes/diabetic complications, and to assess the evidence for the modulatory effects on inflammatory signals and therapeutic potential of a large array of food- and herb-derived phytochemicals in diabetes and its micro/macro vascular complications.

2. Autoimmune-mediated inflammation as a pivotal modulator of T1DM progression

The prevalence of T1DM in children and adolescents has markedly increased in developing and developed countries over the past ten years and now accounts for 5% of all patients with diabetes [14]. An autoimmune response consequent to the interplay of a large array of genetic and environmental factors acts as the key mediator in the induction of impaired β -cell survival and defective insulin secretion [15]. Infiltration of pancreatic islets by effector immune cells, including CD4⁺ and CD8⁺ T cells, macrophages, dendritic cells, and B cells has been shown to be dramatically enhanced in T1DM [16]. Notably, cytotoxic T cells are believed to be the key players, predominantly initiating and amplifying the progress of T1DM. Monocytes and macrophages isolated from T1DM patients exhibit enhanced production of pro-inflammatory cytokines, consistent with evidence from rodent models that show a marked increase in circulating levels of proinflammatory cytokines (IL-1 β , IL-6, and TNF- α) [17]. Inflammatory cytokines mediate the damage to pancreatic β -cells by cytotoxic effects. Contrary to α cells, pancreatic β cells possess a high abundance of receptors specific for various cytokines and significantly contribute to enhanced susceptibility to cytokine-induced cytotoxicity and subsequent cell death [18].

3. Metabolic inflammation as the key driving force in T2DM development

T2DM is the most common form within the spectrum of diabetes, accounting for around 90 % of all cases [19]. It has been documented as the third most common risk factor for disability-adjusted life years worldwide [20]. Furthermore, T2DM-related medical expenditure in low- and middle-income countries is predicted to become up

to three times greater than that for the general population [21]. The pathogenesis of T2DM is multifactorial. Peripheral insulin resistance gives rise to elevated glucose production in the liver and reduced glucose consumption by skeletal muscle and adipose tissue. This together with marked β -cell dysfunction ultimately leads to hyperglycemia [22]. An increase in glucose levels and free fatty acids may promote activation of the inflammatory response in pancreatic islet cells, contributing to the elevated production of pro-inflammatory cytokines. Initially, macrophage-derived IL-1 β can stimulate insulin secretion, which is compensatory for the insulin resistance, and promote β -cell proliferation. Nonetheless as it becomes prolonged or excessive, IL-1 β will induce the production of a wide range of cytokines and chemokines such as IL-6, IL-8, IL-33. These recruit macrophages and immune cells to the islet and further initiate a vicious cycle of IL-1 β auto-stimulation [23]. Furthermore, these macrophages can produce a high level of IL-1 β and cytotoxic factors that combined with the molecular pathways, leading to the definitive decrease in β -cell mass and impaired function [24,25] (Fig. 1).

4. Complications of diabetes

Poorly controlled diabetes can cause a host of complications, ranging from heart disease, stroke, kidney disease, nerve damage, eye damage, digestion problems, erectile dysfunction, skin problems, high susceptibility to infection, to dental problems. It has been well established that the progression of diabetic complications results from the interplay of multiple factors, among which metabolic inflammation represents a key player. Excessive inflammation can seriously accelerate tissue injury *via* pro-inflammatory modulators that are regulated by nuclear transcription factor, nuclear factor-kappa-B (NF- κ B) [26] (Fig. 2). Specifically, diabetes-evoked inflammation functions as a trigger for the development of vascular damage, which plays a central role in mediating the progression of microvascular complications, including diabetic kidney disease, diabetic retinopathy and diabetic neuropathy [27,28]. Diabetes-evoked chronic low-grade inflammation is the focus of research aiming to understand the pathogenesis of microvascular complications of T2DM (Fig. 3).

4.1. Diabetic kidney disease

Diabetic kidney disease (DKD) represents one of the most common chronic micro- and macrovascular complications and leading cause of end-stage renal failure in patients with diabetes [29,30]. Notably, the incidence of DKD in patients with T1DM and T2DM is 40–50 % and 30 %, respectively. Therefore, DKD causes a heavy global disease burden [31]. It is clinically characterized by progressive proteinuria with a marked decline in glomerular filtration rate, both of which indicate deteriorating function of renal nephrons [32]. Diabetes-related hyperglycemia and hypertension play a crucial role in triggering the

pathophysiological development of several events in the kidneys, including glomerular hyperfiltration, glomerular hypertrophy, glomerulosclerosis, and tubulointerstitial inflammation [33,34]. Chronic inflammation has been shown to be a key force that drives the pathogenesis of DKD. A large array of pro-inflammatory cytokines, including IL-1, IL-6, as well as TNF- α , have been shown to be closely associated with the severity of DKD. More importantly, therapeutic strategies that target the inflammatory response and pro-inflammatory cytokines have been shown to be beneficial in

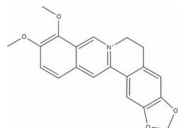
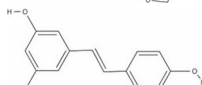
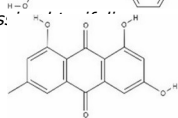
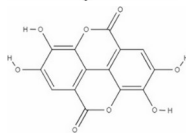
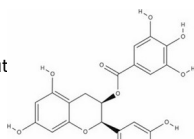
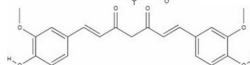
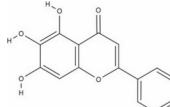
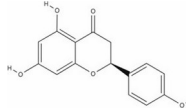
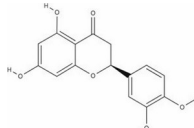
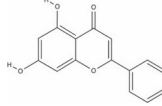
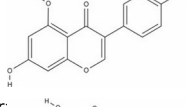
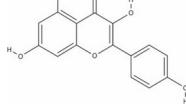
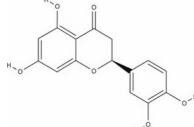
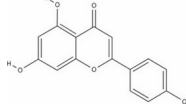
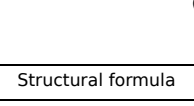
animal models of DKD [35,36], thus offering insight into new therapeutic targets.

4.2. Diabetic retinopathy

Diabetic retinopathy (DR) is the primary cause of blindness in patients with diabetes [37]. The estimated global prevalence of DR with consequent progression of vision-threatening complications is 34 % in subjects with any type of diabetes [38]. Various risk factors have been demonstrated to be strongly related to DR, including longer duration of

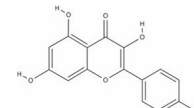
Table 1

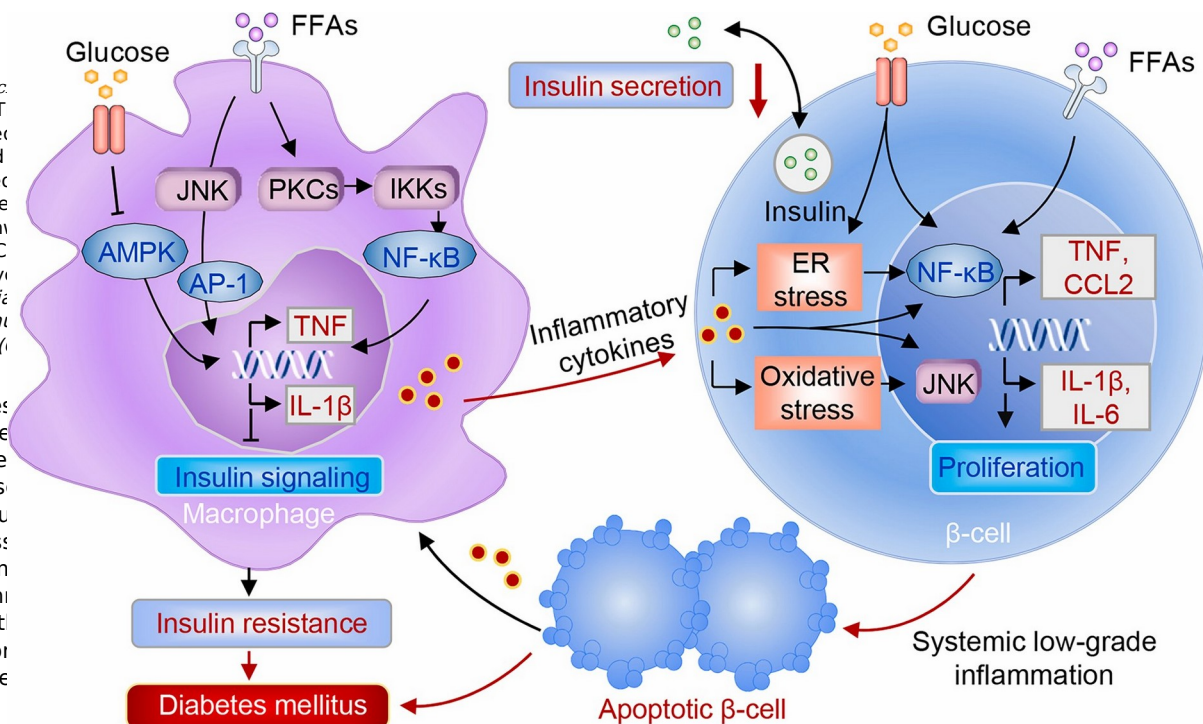
The classifications and chemical structures of phytochemicals in the treatment of diabetes and its complications.

Compound group	Name of compound	Source	Structural formula	References
Alkaloids	Berberine	<i>Rhizoma coptidis</i> <i>Cortex phellodendri</i>		[43]
Non-flavonoid polyphenols	Resveratrol	Grapes, plums, peanuts, nuts, red wine		[52]
	Emodin	<i>Rheum palmatum</i> , <i>Polygonum cuspidatum</i> , <i>Polygonum multiflorum</i> , <i>Cas.</i>		[66]
	Ellagic acid	Berries, pomegranate, dried fruit		[70]
	Epigallocatechin gallate	Green tea <i>Camellia sinensis</i> , strawberries, blackberries, kiwis, cherries, pears, peaches, apples, avocados, pecans, pistachios, hazelnut		[77]
	Curcumin	<i>Curcuma longa</i>		[87]
	Baicalein	<i>Scutellaria</i>		[93]
	Naringenin	Citrus fruits, tomatoes, cherries, grapefruit, cocoa		[96]
	Hesperetin	Orange, lemon		[108]
	Chrysin	Passion fruit, honey, propolis		[116]
	Genistein	Legumes		[123]
Flavonoid polyphenols	Kaempferol	Tea, leek, onion, chives, beans, broccoli, mustard, cucumber, tomato, grape, raspberry, strawberries, peach, apples, cowberries, <i>Centella asiatica</i> , <i>Lycium barbarum</i> , <i>Crocus sativus</i>		[131]
	Eriodictyol	<i>Eriodictyon californicum</i>		[136]
	Apigenin	Grapefruit, oranges, onions, parsley, wheat sprouts, tea, chamomile		[141]
	Quercetin	Apples, black tea, berries, capers, red wine, onions		[145]

(continued on next page)

Table 1 (continued)

Compound group	Name of compound	Source	Structural formula	References
				



4.3. Diabetic peripheral neuropathy

Diabetic peripheral neuropathy (DPN) is a severe chronic complication that affects more than 50 % of diabetic individuals [39]. It selectively occurs in the sensory and autonomic nervous system. The progression of DPN is closely associated with hyperglycemia, insulin deficiency/resistance [40] and dyslipidemia [41]. DPN promotes the development of vascular complications characterized by elevated activity of the polyglut pathway, activation of protein kinase C, and

natural compounds with potential for further development as new therapies for diabetes and its complications. Metabolic inflammation that underlies the pathogenesis of diabetes and its complications is characterized by dramatically enhanced production of various pro-inflammatory cytokines (such as TNF- α , ILs) and chemokines (such as chemokine C-C motif ligand-2 and 5). Herb-derived natural compounds with anti-inflammatory effects and mechanistic insight into their potential for the treatment of diabetes and its complications are summarized in Table 2.

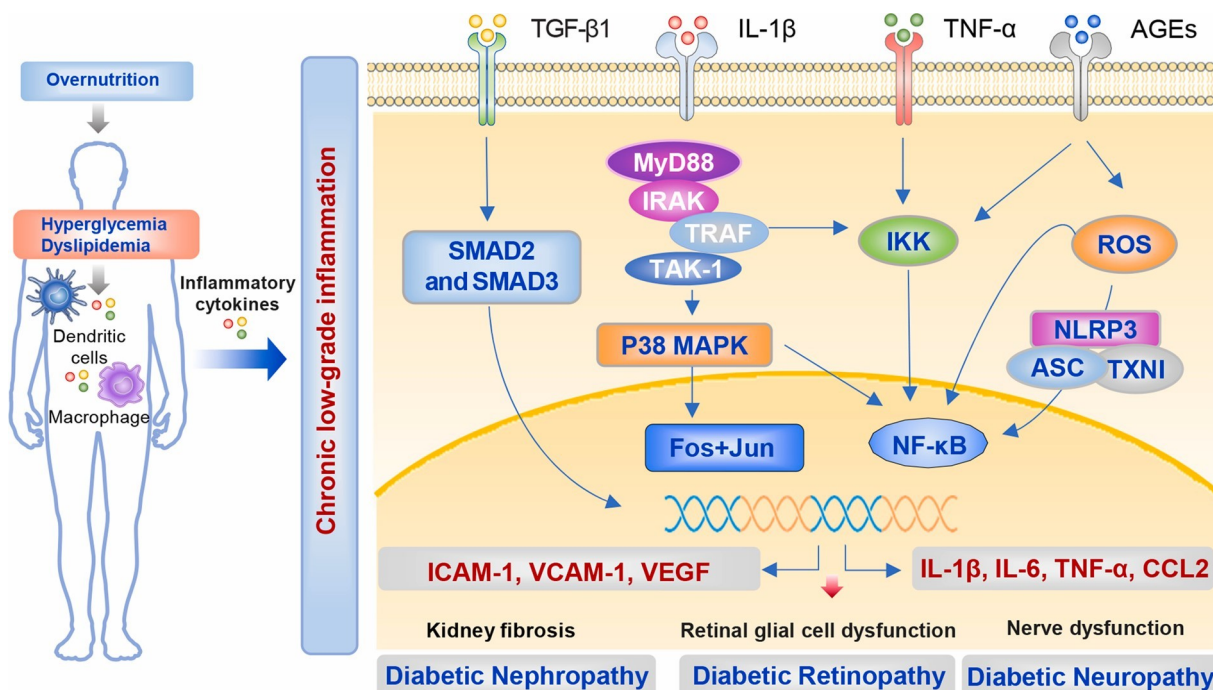


Fig. 2. Chronic and systemic effects of inflammation induced by hyperglycemia and dyslipidemia on the pathology of diabetic complications.

Overnutrition and obesity promote hyperglycemia and dyslipidemia. Chronic hyperglycemia and dyslipidemia activate macrophages and dendritic cells that release pro-inflammatory cytokines such as IL-1 β and TNF- α and amplify the inflammatory response. Chronic, low-grade inflammation due to the activation of various signaling pathways (such as NF- κ B and p38 MAPK) induces a plethora of adverse effects including progressive kidney fibrosis, retinal glial cell dysfunction and

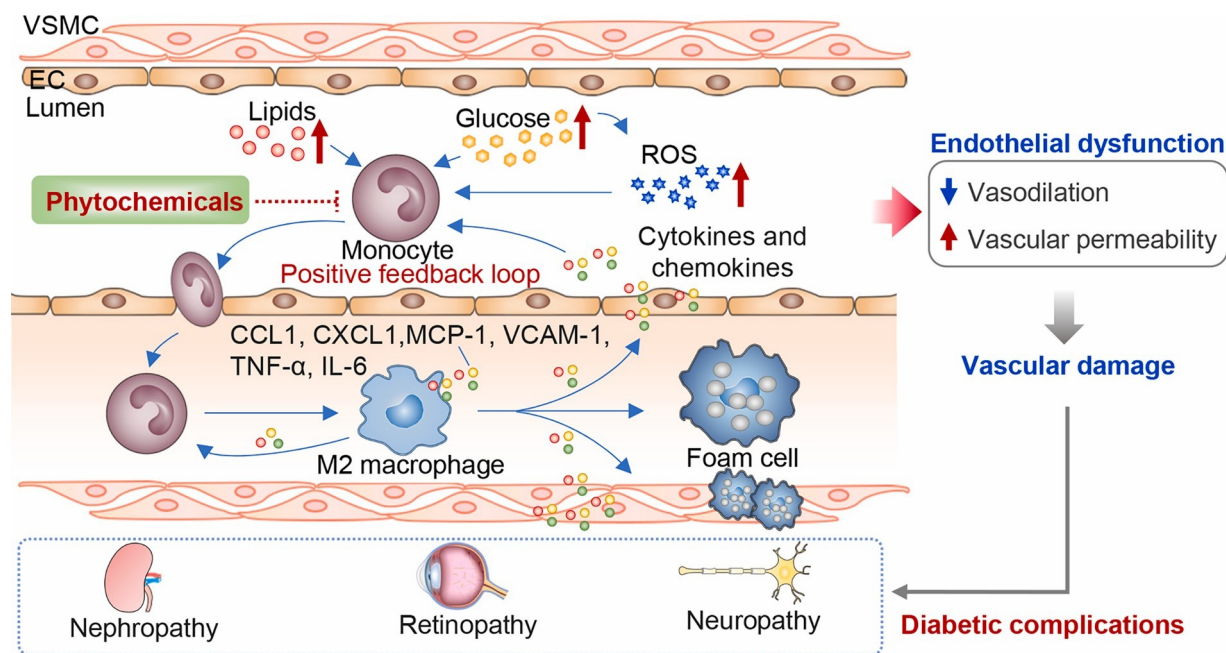


Fig. 3. Inflammatory mechanisms linking diabetes-induced vascular damage and the development of diabetic complications. Hyperglycemia co-existing with hyperlipidemia, elevate proinflammatory cytokines (IL-6, TNF- α , etc) and chemokines (CCL1, CXCL1, etc) and reactive oxygen species potentiates monocyte adhesion and releases of pro-inflammatory modulators, which further enhances vascular recruitment of monocyte and inflammatory response through positive feedback manner. Hyperglycemia-evoked vascular inflammation potentiates endothelial dysfunction (blunted vasodilation and increased vascular permeability) and triggers vascular damage, thereby promoting the development of various diabetic complications, such as diabetic kidney disease, diabetic retinopathy and diabetic peripheral neuropathy. (Abbreviations. CCL1, C-C motif chemokine ligand 1; CXCL1, C-X-C motif chemokine ligand 1; EC, endothelial cells; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; ROS, reactive oxygen species; TNF- α , tumor necrosis factor; VSMC, vascular smooth muscle cells).

Table 2
 Anti-inflammatory mechanisms corresponding to the benefits of representative phytochemicals in experimental models of diabetes and its complications.

Compound	Animal Models (Effective dose)	Cell Experiments (Effective concentration)	Main results		Effects	References
			Upregulation	Downregulation		
Berberine	Diabetes (50/100/150/500 mg/kg) Diabetic kidney disease (200 mg/ kg)	-	-	C reactive protein, NF- κ B activation, ICAM-1, TGF- β 1, TNF- α , IL-1 β , IL-6, MCP-1, iNOS, COX-2	Inhibition of adipocyte differentiation, reduction of low-density lipoprotein cholesterol, anti-inflammation, anti-diabetes	[45,46,47]
Resveratrol	Diabetes (5/20 mg/kg) Diabetic retinopathy (0.1/0.5/5/50 mg/kg) Diabetic kidney disease (1/5 mg/kg) Obesity (80 and 480 mg/day)	ARPE-19 cells (1.25/2.5/5/10 μ M) RRECs (10/50/100 μ M)	SIRT1 activity	NF- κ B activation, TNF- α , IL-1 β , IL-6, IL-8, IL-10, COX-2, TGF- β , VEGF, IFN- γ , MCP-1, AMPK dephosphorylation, ICAM-1, VCAM-1	Antidiabetic, anti-obesity, anti- cancer, neuroprotective and cardioprotective effects	[55,56,57,58, 59,60,61,62, 63,64,65]
Emodin	-	C2C12 myotubes (25 μ mol/ L) 3T3-L1 adipocytes (25 μ mol/L) HUVECs (3 μ M)	-	CCL5, activation of NF- κ B, p38 MAPK and ERK1/2	Anti-tumor activity, anti-inflammation, anti-diabetes	[68,69]
Ellagic acid	Diabetic kidney disease (20/40/50/100/150 mg/kg) Diabetic peripheral neuropathy (50 mg/kg)	NRK 52E cells (0.5 μ M/100 μ g/L)	-	NF- κ B activation, IL-1 β , IL-6, TNF- α , the HMGB1-TLR4-NF- κ B pathway	Anti-diabetes, antioxidation, anti-inflammation, anti-cancer effects, inhibition of cardiovascular disease and neurodegenerative diseases	[74,75,76]
Epigallocatechin gallate	Diabetes (0.1 % of diet) Diabetic kidney disease (100 mg/kg)	MMCs (50/75/100 μ M) HAECs (1 μ M) Primary vascular endothelial cells	NRF2 signaling	IL-1 β , IL-6, TNF- α , Notch signaling, macrophage	Anti-diabetes, anti-inflammation, antioxidation, cholesterol-lowering effects,	[79,80,81,82, 83,84,85,86]

M. Biomedicine & Pharmacotherapy 133 (2021)	Kong 110975 (25/50 μ M) HUVECs (10/30/ 50 μ M) HepG2 cells (50 μ M) RAW264.7 (20 μ g/mL)			et accumulation, ICAM-1, VCAM-1, NF- κ B activation	cardiovascular protection	
Curcumin	Diabetes (100 mg/kg) Diabetic kidney disease (100 mg/kg)	MPC-5 (1/5/10 μ M)	AMPK and PPAR- γ signaling	NF- κ B activation, TLR4, aveolin-1 Tyr (14) phosphorylation, ROS overproduction, leukocyte- endothelium interaction	Anti-diabetes, antioxidation, anti-inflammation, antihepatotoxic and cholesterol-lowering effects	[88,89,90,91, 92]
Baicalein	Diabetic kidney disease (10/20 mg/kg)	-	IRS1/PI3K/Akt pathway	NF- κ B activation, iNOS, TGF- β 1, the MAPKs pathway	Anti-diabetes, antioxidation, anti-inflammation, anti- cancer effects	[94,95]
Naringenin	Diabetes (50 mg/kg) Diabetic kidney disease (25/50/75 mg/kg) Gestational diabetes mellitus (50/100 mg/kg)	NRK-52E cells (1 μ mol/L) HUVECs (30 μ M)	PPARs, AMPK activation	IL-6, TNF- α , TGF- β , ICAM-1, NF- κ B activation,	Anti-diabetes, anti- inflammation	[97,98,99, 100,101,102, 103,104,105, 106,107]
Hesperetin	Diabetes (40/50 mg/kg) Diabetic kidney disease (50/80/150 mg/kg) Diabetic retinopathy (100 mg/kg)	-	-	TNF- α , IL-1 β , IL-6	Anti-hyperlipidemic, anti- inflammatory, anti-oxidative, anti-diabetic, anti- hypertensive, cardioprotective properties	[110,111,112 , 113,114,115]
Chrysin	Diabetes (50 mg/kg) Diabetic kidney disease (10 mg/kg) Diabetic peripheral neuropathy (30/100 mg/kg)	HMCs (1/10/20 μ M)	PPAR- γ	NF- κ B activation, TNF- α , IL-1 β , IL-6, TGF- β 1, Smad 2/3	Anti-diabetes, anti- inflammation	[117,119,120 , 121,122]
Genistein	Diabetes (1/20 mg/kg) Diabetic kidney disease (10 mg/kg)	HMCs (100 μ M) 3T3-L1 adipocytes (50 μ M)	-	IL-6, TNF- α , C reactive protein, MCP-1, COX-2	Anti-diabetes, anti- inflammation	[124,125,126 , 127,128,129, 130] [132,133,134 , 135]
Kaempferol	Diabetes (150 mg/kg)	-	-	NF- κ B activation	Anti-diabetes, anti- inflammation, cardioprotective effects	[137,138,139 , 140]
Eriodictyol	Diabetic retinopathy (10 mg/kg)	HepG2 cells/differentiated 3T3-L1 adipocytes (5/25 μ M) RGC-5 cells (5/10/ 20 μ M) HMCs (12.5/25 μ M)	PPAR γ 2	TNF- α , IL-8	Anti-diabetes, anti- inflammation, antioxidation	[137,138,139 , 140]
Apigenin	Diabetes (50/100 mg/ kg) Diabetic kidney disease (20 mg/kg) Obesity (100 mg/kg)	HUVECs (3/30 μ M) MEFs (25 μ mol/L)	-	CD38, NF- κ B activation, TNF- α , IL-1 β , IL-6, MAPK activation	Antioxidant, anti-inflammatory, antiapoptotic, antifibrotic and antidiabetic properties	[97,142,143, 144]
Quercetin	Diabetes (10/25/40/50 mg/kg) Diabetic kidney disease (50/100 mg/kg)	RINm5F cells (20 μ M)	Switching macrophages from M1 to M2 polarization	IL-1 β , IL-18, NLRP3 inflammation	Anti-diabetes, anti- inflammation	[146,147,148 , 149,150,151]

5.1. Alkaloids

5.1.1. Berberine

Berberine (2,3-methylenedioxy-9,10-dimethoxyprotoberberine chloride) is an alkaloid and isoquinoline derivative initially isolated from *Rhizoma coptidis* (Huanglian) and *Cortex phellodendri* (Huangbai) and has been widely applied in the treatment of gastroenteritis and diarrhea [43]. Berberine exerts beneficial pleiotropic effects, including inhibition of adipocyte differentiation, lowering of blood levels of low-density lipoprotein cholesterol, and inhibition of inflammation [44]. In diabetic animal models induced by streptozotocin (STZ), berberine treatment significantly decreased circulating blood levels of the chronic inflammatory biomarker C reactive protein, free fatty acids, cholesterol, and triacylglycerols, mainly by inhibiting the activity of dipeptidyl peptidase-4 and protein tyrosine phosphatase-1B (PTP-1B). Meanwhile, berberine enhanced insulin sensitivity, thereby alleviating insulin resistance to lower fasting blood glucose

levels [45]. It also effectively inhibited RhoA/ROCK signaling and decreased transcriptional activity of NF- κ B, accompanied by decreased production of intercellular adhesion molecule-1 (ICAM-1), transformed growth factor beta-1 (TGF- β 1) and fibronectin in models of diabetic nephropathy. In diabetic *db/db* mice, berberine treatment notably blunted the up-regulation of several pro-inflammatory genes in adipose tissue, such as TNF- α , IL-1 β , IL-6, MCP-1, iNOS and COX-2. Berberine has also been shown to markedly combat oxidative stress by suppressing the production of reactive oxygen species (ROS) in glomerular mesangial cells stimulated by high glucose *in vitro* [46]. In non-obese diabetic mice with T1DM-like phenotypes, berberine protected against spontaneous chronic inflammation in the spleen, liver, and kidneys by regulating pro-/anti-inflammatory or Th1/Th2 cytokine expression [47].

Accumulating evidence suggests that the gut microbiome functions as not only a key player in the aetiology of diabetes and related complications, but also an important target for various anti-

diabetic drugs [48]. Likewise, recent evidence suggests that the modulatory effect on gut microbiota is a crucial mechanism that underlies the anti-diabetic benefits of berberine. In a high fat diet-induced mouse model of obesity, berberine treatment lowered blood levels of glucose and lipids in close association with a marked alteration of gut microbiota [49]. Gut microbial metabolites are crucial mediators of the regulatory effect of gut microbiota on the development of metabolic diseases. In a rat model of insulin resistance, berberine treatment modulated structure of the gut microbiota and specifically enhanced the abundance of short-chain fatty acids-producing bacteria (including *Blautia* and *Allobaculum*), thereby boosting fecal enrichment of short-chain fatty acids [50]. The fermentation of branched-chain amino acids (BCAAs) acts as a major contributor to the generation of branched-chain fatty acids that are triggers for metabolic dysfunction. Berberine administration in mice fed a high fat diet significantly attenuated insulin resistance and metabolic inflammation in the liver, closely associated with a notably decreased abundance of BCAA-producing bacteria, including those of the *Clostridiales* order and *Streptococcaceae*, *Clostridiaceae*, and *Prevotellaceae* family as well as *Streptococcus* and *Prevotella* genera [51].

5.2. Non-flavonoid polyphenols

5.2.1. Resveratrol

Resveratrol (3,4',5-trihydroxystilbene), a polyphenolic phytoalexin, is present in many plants including grapes, plums, peanuts and nuts [52]. It has been extensively studied in the treatment of various diseases owing to its multiple pharmacological properties, including, but not limited to, antidiabetic, anti-obesity, anti-cancer, neuroprotective and cardioprotective effects [53,54]. Long-term treatment with resveratrol has been shown to attenuate activation of NF- κ B and up-regulate pro-inflammatory mediators (such as TNF- α , IL-6, and COX-2) in rats with STZ-induced diabetes [55–57]. Specifically, resveratrol alleviated retinal inflammation, thereby improving diabetic retinopathy. In retinal cells under hyperglycemic conditions, resveratrol reduced the expression of TGF- β , vascular endothelial growth factor (VEGF), IL-6, and IL-8 in a dose-dependent manner, all of which have been well documented to potentiate the progression of diabetic retinopathy [58]. In a rat model of STZ-induced diabetic retinopathy, resveratrol significantly attenuated retinal damage mainly through its potentiating effect on paraoxonase-1 expression and inhibitory effects on ox-DLD, retinal AGEs, and inflammatory cytokines (IL-1 β , IL-6, TNF- α , IFN- γ , MCP-1 and VEGF) [59]. Resveratrol also significantly reversed retinal AMP-activated protein kinase (AMPK) dephosphorylation, sirtuin 1 (SIRT1) inactivation, and NF- κ B phosphorylation in STZ-induced diabetic mice. Notably, diabetic-induced retinal leukocyte adhesion as well as ICAM-1 and VEGF expression were reduced following administration of resveratrol [60]. Additionally, resveratrol protected against

cerebral ischemia/reperfusion injury in diabetic rats, principally by alleviating oxidative stress and inflammation [61].

Resveratrol has shown therapeutic promise in experimental models of diabetic kidney disease largely due to its anti-inflammatory effects. Resveratrol ameliorated renal dysfunction in close association with reduced renal production of pro-inflammatory cytokine IL-1 β in diabetic rats [62]. Oral administration of resveratrol significantly blocked the elevated levels of TNF- α , IL-1 β , IL-6 and NF- κ B p65 subunits in the kidneys of diabetic rats, thereby ameliorating inflammation-mediated kidney damage in DKD [63]. Additionally, resveratrol has been reported to play a protective role in diabetes-induced vascular complications. Dietary supplementation with resveratrol markedly lowered blood levels of glucose and lipids in diabetic *db/db* mice. Furthermore, the beneficial effects of resveratrol on systemic metabolic profiles were accompanied by vascular protection afforded through inhibited expression of ICAM-1, endothelial vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemoattractant protein-1 (MCP-1) in the aorta [64]. More importantly, the beneficial effects of resveratrol in diabetes and its complications that were evidenced in rodent models were further supported by data from rhesus monkeys fed a high-fat, high-sugar diet. They demonstrated marked improvement of metabolic disorders following administration of resveratrol for 2 years, evidenced by the restoration of adipocyte size, up-regulation of SIRT1, and improved insulin sensitivity in visceral white adipose tissue [65]. Taken together, resveratrol has demonstrated pleiotropic benefits in the treatment of experimental models of diabetes and its related microvascular complications in the eyes and kidneys, largely through modulation of the inflammatory response.

5.2.2. Emodin

Emodin (1,3,8-trihydroxy-6-methylanthraquinone), a polyphenol that is mainly extracted from *Rheum palmatum*, *Polygonum cuspidatum*, *Polygonum multiflorum*, and *Cassia obtusifolia*, is well-known as the bioactive component of laxative herbs. It also has anti-tumor and anti-inflammatory effects [66]. Specifically, a growing body of evidence supports the potential of emodin to treat diabetes and its complications [67]. Emodin exhibited a regulatory effect on glucose metabolism, evidenced by *in vitro* data that showed enhanced glucose uptake and consumption in C2C12 myotubes and 3T3-L1 adipocytes through regulation of the AMPK signaling pathway. Moreover, emodin increased glycolysis, but inhibited lipolysis in close association with significantly decreased phosphorylation of perilipin in 3T3-L1 adipocytes. Mechanistically, emodin inhibited the activation of NF- κ B and ERK pathways in C2C12 myotubes and 3T3-L1 adipocytes [68]. Emodin has also been shown to protect against diabetes-induced vascular inflammation and endothelial dysfunction. In the presence of diabetes, high glucose evoked overexpression of chemokine (C-C motif) ligand 5 (CCL5), a chemokine that contributes to the recruitment of

pro-inflammatory cells in blood vessels and early damage to endothelial cells. Emodin protected endothelial cells against high glucose-evoked apoptosis and vascular inflammation largely by inhibiting CCL5 expression and phosphorylation of ERK 1/2 and p38 mitogen-activated protein kinase (MAPK) [69]. Emodin represents a potential therapeutic agent for diabetes and its associated endothelial disorders.

5.2.3. Ellagic acid

As a product of hydrolyzed tannins, ellagic acid (2,3,7,8-tetrahydroxy-chromeno) is mainly present in berries, pomegranate and dried fruit [70]. It has been proposed in the treatment of various chronic diseases such as cardiovascular disease [71] and neurodegenerative diseases [72], predominantly dependent on its multiple remarkable biological effects including antioxidant, anti-inflammatory and anticancer activities [73]. Intriguingly, recent data support ellagic acid as a notable anti-diabetic compound. In a rat model of type 2 diabetes and its related kidney injury, ellagic acid treatment significantly combated hyperglycemia, insulin resistance and diabetic nephropathy, largely by inhibiting the activation of NF- κ B. This protective effect was closely associated with a markedly suppressed inflammatory response, evidenced by notably lowered serum levels of pro-inflammatory cytokines (IL-1 β , IL-6, and TNF- α) [74]. More recently, it has been reported that chronic treatment with ellagic acid improved anxiety/depression-like behavior, enhanced exploratory/locomotor activities, and largely restored cognitive capacity in diabetic rats. Mechanistically, the beneficial effects of ellagic acid were accompanied by improved hyperglycemia, notable modulation of inflammatory status and amelioration of neuronal loss [75]. Specifically, ellagic acid treatment significantly alleviated hyperglycemia-evoked renal injury in DKD mice by inhibition of the high mobility group box 1-toll-like receptor 4-NF- κ B pathway [76], further supporting an anti-inflammatory effect as one of the key mechanisms underlying the protective effect of ellagic acid in diabetes and a wide spectrum of complications.

5.3. Flavonoid polyphenols

5.3.1. Epigallocatechin gallate

Epigallocatechin gallate is a natural constituent predominantly found in green tea but also a broad variety of food, plants and herbs, including cranberries, strawberries, blackberries, kiwis, cherries, pears, peaches, apples, avocados, pecans, pistachios, and hazelnuts [77]. Extensive exploration has demonstrated numerous health benefits, including attenuation of inflammation, weight loss, lowered circulating levels of cholesterol, and cardiovascular protection [78]. Epigallocatechin gallate has also emerged as a potential anti-diabetic agent. Treatment with epigallocatechin gallate has been shown to improve wound healing in STZ-induced diabetic mice in close association with reduced levels of pro-inflammatory mediators (including IL-1 β , TNF- α and

IL-6) and inhibition of Notch signaling and macrophage accumulation at a wound site [79]. Mechanistically, epigallocatechin gallate inhibited high glucose-induced upregulation of VCAM-1 and ICAM-1 in the mouse kidney with diabetic nephropathy and high glucose-stimulated mesangial cells by promoting activation of nuclear factor E2-related factor 2 (NRF2) that functions as a master regulator of oxidative stress and inflammation [80,81]. Epigallocatechin gallate also acted as a potent anti-oxidant in human hepatocellular liver carcinoma cells (HepG2) to attenuate oxidative stress by inhibiting the production of ROS and promoting the activity of antioxidant enzymes superoxide dismutase and glutathione peroxidase. Thus, epigallocatechin gallate has shown beneficial effects on oxidative stress-related insulin resistance and inflammation in HepG2 cells [82]. Moreover, epigallocatechin gallate protected against cardiovascular complications in a rat model of diabetes-induced cardiovascular injury by decreasing circulating levels of pro-inflammatory mediators (TNF- α , IL-1 β and IL-6) and endothelial adhesion molecules (ICAM-1 and VCAM-1) [83]. Additionally, epigallocatechin gallate suppressed vascular inflammation by inhibiting NF- κ B activation in genetically diabetic *db/db* mice and human umbilical vein endothelial cells [84,85]. Dietary supplementation with epigallocatechin gallate at a low concentration (0.1 %) has been shown to suppress hyperglycemia-evoked inflammation in the adipose tissue of Goto-Kakizaki rats, a polygenic non-obese strain that develops adult-onset type 2 diabetes early in life [86]. Collectively, epigallocatechin gallate shows potential as a novel agent for diabetes, principally because of its anti-inflammatory properties.

5.3.2. Curcumin

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadine-3,5-dione] is a polyphenol compound predominantly found in the rhizome of *Curcuma longa*. It is also the active ingredient of the dietary spice turmeric. Curcumin has been shown to exert anti-inflammatory, antihepatotoxic and cholesterol lowering properties [87]. Most intriguingly, there is mounting evidence that supports curcumin as a promising treatment for diabetes and its complications. A dietary curcumin admixture has been shown to ameliorate glucose intolerance and insulin resistance in high-fat diet-induced obese and leptin-deficient *ob/ob* mice. The metabolic benefits of curcumin were accompanied by reduced macrophage infiltration of white adipose tissue, increased production of adiponectin in adipose tissue, and decreased NF- κ B activity in the liver [88]. In genetically engineered diabetic *db/db* mice, curcumin exhibited potent effect on the coordination of inflammatory regulator NF- κ B and metabolic modulators AMPK and peroxisome proliferator-activated receptor gamma (PPAR- γ) [89]. Treatment with curcumin for twelve weeks attenuated histological lesions and fibrosis and inhibited expression of pro-inflammatory genes in the rat kidney with streptozotocin-induced diabetic nephropathy. Moreover, curcumin treatment blunted caveolin-1 Tyr (14) phosphorylation and

down-regulated the expression of toll-like receptor (TLR4) in both the rat kidney and high glucose-stimulated podocytes, indicating that inhibition of renal inflammation *via* blockade of caveolin-1 Tyr (14) phosphorylation and TLR4 activation were the key mechanisms corresponding to the benefits of curcumin in alleviating diabetic nephropathy [90]. In addition, curcumin ameliorated dysfunction of pancreatic β cells by inhibiting the inflammatory response and cellular stress signals in endoplasmic reticulum and mitochondria to prevent apoptosis [91]. Curcumin treatment also improved diabetes-induced vascular inflammation by suppressing overproduction of ROS and the interaction between leukocytes and endothelium [92]. These data promote curcumin as a novel candidate therapy for T2DM and its complications, and warrants further investigation.

5.3.3. Baicalein

Baicalein (5,6,7-trihydroxy-2-phenyl-4H-1-benzopyran-4-one) is one of the key bioactive flavonoids initially isolated from the root of *Scutellaria* [93]. Among its numerous biological functions, the metabolic benefits of baicalein are being extensively investigated. In rat models of diabetes induced by the combination of a high fat diet and STZ, baicalein treatment for 16 weeks effectively decreased blood glucose levels and increased insulin sensitivity. In addition, baicalein supplementation significantly restored glucose metabolism and reduced insulin resistance. Furthermore, baicalein treatment significantly improved histological lesions of the kidney by downregulating the release of inducible nitric oxide synthase (iNOS) and TGF- β 1, and repressing the NF- κ B-mediated inflammatory response [94].

In mice with high fat diet-induced metabolic syndrome, baicalein treatment effectively ameliorated multiple co-existing metabolic disorders including glucose intolerance, insulin resistance, excessive body weight gain, dyslipidemia, and abnormal fat deposition within hepatocytes. Mechanistically, baicalein's inhibitory effect on inflammation and insulin resistance was largely dependent on its inhibitory effect on the MAPKs pathway and activation of the IRS1/PI3K/Akt pathway. [95]. Among the many pleiotropic biological benefits, its anti-diabetic properties offer the most potential for drug development along with its other antioxidant, anti-inflammatory and anti-cancer effects.

5.3.4. Naringenin

Naringenin [5,7-Dihydroxy-2-(4-hydroxyphenyl)chroman-4-one] is a flavanone predominantly present in citrus fruit and grapefruit [96]. Mounting evidence suggests that naringenin is a potential anti-diabetic agent. In a rat model of T2DM, naringenin ameliorated hyperglycemia, insulin resistance, and hyperlipidemia [97]. In mice with glucose intolerance during pregnancy, treatment with naringenin lowered blood glucose levels in close association with enhanced membrane translocation of insulin-responding glucose transporter GLUT4 and glucose uptake through the AMP-activated protein kinase (AMPK) pathway in skeletal muscle

cells [98]. Naringenin also inhibited gluconeogenesis through upregulation of AMPK, similar to metformin, and mitigated inflammation and cell proliferation [99].

Naringenin has shown strong potential to attenuate vascular complications of diabetes. Administration has improved diacetate-induced renal damage and the abnormal altered lipid profile in a mouse model of diabetic nephropathy. Its benefit was largely dependent on its up-regulation of the transcriptional abundance of PPARs and reduction of mRNA levels of pro-inflammatory TNF- α and IL-6 [100,101]. Naringenin treatment also decreased blood levels of endothelial adhesion molecules ICAM-1 coupled with marked restoration of phenylephrine-mediated contractions and acetylcholine or insulin-induced relaxation of aortic tissue in T2DM rats. *In vitro* data demonstrated that naringenin suppressed activation of master transcription factor NF- κ B and down-regulated mRNA expression of ICAM-1 in palmitic acid-induced endothelial cells, further providing mechanistic insight into the cardiovascular protective role of naringenin [97].

Mechanistic investigations have revealed inflammation as one of the key targets corresponding to the beneficial effects of naringenin. In diabetic rats who were given naringenin, hyperglycemia-mediated inflammation was reduced in hepatic and pancreatic tissue samples [102,103]. Likewise, naringenin induced notable suppression of circulating levels of pro-inflammatory cytokines including TNF- α , IL-6, TGF- β and ICAM-1 in pregnant diabetic rats [104]. *In vitro* data demonstrated that incubation with naringenin markedly inhibited the expression of pro-inflammatory cytokines and chemokines in human placenta and visceral adipose tissue stimulated by inflammation inducer TNF- α [105]. More specifically, naringenin attenuated the inflammatory response of macrophages and neutrophils that are key players in modulating the innate immune response of adipose and other metabolic tissues [106, 107].

5.3.5. Hesperetin

Hesperetin (3',5,7-trihydroxy-4-methoxyflavanone), the aglycone of hesperidin, is the flavanone that is predominantly abundant in citrus fruits such as orange and lemon [108]. Multiple pharmacological effects have been identified for hesperetin including anti-hyperlipidemic, anti-inflammatory, anti-oxidative, anti-diabetic, anti-hypertensive, and cardioprotective properties [109]. In a rodent model of STZ-induced diabetes, hesperetin attenuated hyperglycemia by reducing oxidative stress and suppressing production of pro-inflammatory cytokines TNF- α and IL-6 [110-112]. Additionally, hesperetin exerted a protective effect against diabetic nephropathy and retinopathy. Oral administration of hesperetin in streptozotocin-induced diabetic rats attenuated diabetes-elicited morphological and functional abnormalities in the kidney in close association with modulatory effects on the AGEs/RAGE axis and TGF- β 1-ILK-Akt signaling pathway [113,114]. Likewise, hesperetin treatment

prevented progression of diabetic retinopathy, largely dependent on its ability to downregulate the expression of pro-inflammatory cytokines TNF- α and IL-1 β in the retina [115]. Hence, hesperetin exhibits notably inhibitory effects on the inflammatory response and may serve as a dietary supplement in the treatment of diabetes and its complications.

5.3.6. Chrysin

Chrysin (5,7-dihydroxyflavone) is one of the major flavonoids present in medical plants, honey and propolis [116]. Chrysin is emerging as a tantalizing agent for the prevention and treatment of diabetes and its complications owing to its promising anti-diabetic and anti-inflammatory properties. In athymic nude diabetic mice, chrysin treatment lowered blood levels of glucoses in close association with reduced circulating levels of pro-inflammatory cytokine IL-1 β and TNF- α [117]. PPAR- γ has been well demonstrated as a master regulator of the metabolic homeostasis of energy, lipid, and glucose. Accordingly, PPAR- γ represents a key target for the development of novel antidiabetic drugs [118]. Promisingly, mounting evidence supports chrysin as a PPAR- γ agonist to exert metabolic benefits. In a rat model of fructose-induced insulin resistance and vascular complications, chrysin attenuated the elevation of systolic blood pressure *in vivo* and alleviated vasoconstriction *in vitro*, largely dependent on the action of PPAR- γ [119]. Likewise, chrysin ameliorated isoproterenol-induced myocardial injury in diabetic rats in close association with enhanced PPAR- γ activation and marked inhibition of oxidative stress and vascular inflammation [120]. Additionally, chrysin exhibited a protective effect on microvascular complications, as demonstrated by the reduction in the recruitment of collagen fiber and α -smooth muscle actin in kidney from *db/db* mice with chrysin treatment. *In vitro* results showed that pretreatment with chrysin blocked activation of TGF- β 1 and Smad 2/3 in kidney mesangial cells [121]. Furthermore, chrysin blocked diabetes-associated cognitive decline in diabetic rats. The neuroprotective effect of chrysin was accompanied by inhibition of inflammatory signals, including blunted activation of NF- κ B and suppressed pro-inflammatory cytokines (IL-1 β , IL-6 and TNF- α) in the cerebral cortex and hippocampus of STZ-induced diabetic rats [122].

5.3.7. Genistein

Genistein (4,5,7-trihydroxyisoflavone) is an isoflavone predominantly derived from legumes [123]. Initially, genistein was shown to be a tyrosine kinase inhibitor with potent ability to suppress insulin-stimulated glucose oxidation in a dose-dependent manner and to block the inhibitory effect of insulin on isoproterenol-stimulated lipolysis. Intriguingly, genistein did not suppress directly insulin-evoked insulin receptor tyrosine autophosphorylation or tyrosine phosphorylation of the cellular substrates [124]. Furthermore, genistein blocked insulin-induced glucose uptake in 3T3-L1 adipocytes [125]. Meanwhile, it suppressed insulin-elicited GLUT4 translocation in mature adipocytes

differentiated from mouse MC3T3-G2/PA6 cells [126]. Consistent with the modulatory effects that genistein revealed *ex vivo*, *in vivo* studies also proposed anti-diabetic benefits. In male non-obese diabetic mice with T1DM-like phenotypes, genistein treatment significantly lowered blood glucose levels. The beneficial effects of genistein were accompanied by activation of the anti-inflammatory response coupled with alteration of β -diversity in gut microbiota [127]. Subcutaneous administration of genistein attenuated pancreatic inflammation and tissue injury in diabetic rat models induced by high fat diet feeding and/or estrogen deficiency [128]. Meanwhile, genistein administration in alloxan-induced diabetic rats improved morphology of the pancreas and intestine in close association with suppressed inflammatory responses, evidenced by reduced circulating levels of IL-6, TNF- α and C-reactive protein [129]. In addition, genistein exhibited a reno-protective benefit, largely dependent on its modulating effects on the diabetes-induced inflammatory response in the kidney. Genistein treatment dampened various pro-inflammatory cytokines in the diabetic kidney, including MCP-1, COX-2, and TNF α [130].

5.3.8. Kaempferol

Kaempferol [3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one] is a typical dietary flavonoid present in tea and various vegetables and fruits, including leek, onion, chives, beans, broccoli, mustard, cucumber, tomato, grapes, raspberry, strawberries, peach, apples and cowberries. More importantly, it is abundant in several Chinese medicinal herbs such as *Aloe vera*, *Centella asiatica*, *Lycium barbarum*, and *Crocus sativus* [131]. Among the numerous benefits of kaempferol, the potential to combat diabetes is supported by a growing body of evidence. Studies have shown that treatment with kaempferol glycoside fractions resulted in decreases in body weight gain, blood glucose, and triglyceride levels, together with improved insulin resistance in mice fed a high fat diet [132]. Likewise, kaempferol administration in diabetic rats ameliorated insulin resistance in close association with inhibition of NF- κ B-mediated hepatic inflammation [133]. In addition, kaempferol has been demonstrated to exert cardioprotective effects: in diabetic rats, it protected the animal from myocardial ischemia-reperfusion injury by attenuating oxidative stress and inflammation in heart tissue [134]. Intriguingly, recent data demonstrated wound healing effects of kaempferol, evidenced by the accelerated healing in diabetic excisional and nondiabetic incisional wounds treated with kaempferol ointment for 14 days [135].

5.3.9. Eriodictyol

Eriodictyol [2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-2,3-dihydrochromen-4-one] is one of the most abundant dietary flavonoids with selective enrichment in *Eriodictyon californicum*. Eriodictyol has been demonstrated to have anti-inflammatory and antioxidant properties [136]. In both HepG2 and differentiated 3T3-L1 adipocytes in the presence of high glucose, eriodictyol augmented

insulin-stimulated glucose uptake in close association with upregulation of PPAR γ 2 and adipocyte-specific fatty acid-binding protein [137]. Eriodictyol treatment decreased the level of cytokines, adhesion molecule, and nitric oxide synthase in the retina of diabetic rats in a dose-dependent manner. Diabetes-related lipid peroxidation was also inhibited [138]. *In vitro* data showed that eriodictyol exerted protective effects on the decreased cell viability of rat retinal ganglion cells stimulated with high glucose in a dose-dependent pattern, accompanied by inhibited production of pro-inflammatory cytokines TNF- α and IL-8 [139]. Incubation with eriodictyol also suppressed high glucose-induced cell proliferation and the release of ROS and pro-inflammatory cytokines in mesangial cells. The latter was a key factor in the pathogenesis of diabetic nephropathy, regulating the formation and maintenance of the glomerular capillary tuft and homeostasis of the mesangial matrix [140]. Therefore, recent data suggested an emerging role for eriodictyol in the treatment of diabetes and its microvascular complications, and warrants further investigation in animal studies.

5.3.10. Apigenin

Apigenin (4',5,7-trihydroxyflavone) is a flavonoid of the flavone family. It is abundant in various fruits, vegetables and herbs, such as grapefruit, oranges, onions, parsley, wheat sprouts, tea and chamomile [141]. It possesses antioxidant, anti-inflammatory, antiapoptotic, antifibrotic and antidiabetic properties. Apigenin has been characterized as a potent pharmacological inhibitor of CD38, the master regulator of extracellular NAD $^{+}$ pools. Administration to obese mice increased NAD $^{+}$ levels, decreased global protein acetylation, and restored homeostasis of glucose and lipid metabolism, supporting apigenin as a plausible agent to treat diabetes and its related metabolic diseases *via* NAD $^{+}$ -dependent pathways [142]. Additionally, apigenin holds great promise in prevention of diabetes-related complications. In rodent models of diabetic cardiomyopathy, treatment with apigenin improved endothelial dysfunction and heart injury by mitigating oxidative stress and inflammation in the heart. Mechanistically, the cardioprotective role of apigenin was closely associated with an inhibitory effect on activation of the inflammatory trigger NF- κ B and the release of pro-inflammatory mediators IL-1 β , IL-6 and TNF- α [97,143]. Apart from the cardiovascular system, apigenin benefits diabetes-evoked injury in the kidney. In a rat model of diabetic nephropathy, apigenin treatment alleviated renal dysfunction, inflammation, oxidative stress, and glomerulosclerosis in close association with significant blockade of MAPK in the kidney [144].

5.3.11. Quercetin

Quercetin (3,3',4',5,7-pentahydroxy-flavone) is a polyphenolic flavonoid abundant in a variety of foods including apples, black tea, berries, capers, red wine, and onions [145]. There is growing evidence of its therapeutic potential in the prevention and treatment of diabetes. Quercetin

has been shown to attenuate oxidative stress to exert protective effects on cytokine-induced injury in pancreatic β cells, the unique source of insulin [146]. Given that diabetes frequently co-exists with non-alcoholic fatty liver disease (NAFLD), the benefit of quercetin in T2DM-induced NAFLD in animal models provides additional insight into the pleiotropic activities of quercetin in the treatment of diabetic complications [147]. Likewise, quercetin treatment exhibited a notably suppressive effect on the release of IL-1 β and IL-18 from the kidney in rats, thereby preventing progression of diabetic nephropathy. This renoprotective role was closely associated with inhibition of activation of NLRP3 inflammatory bodies that acted as a key player in the regulation of maturation of IL-1 β and IL-18 [148]. Furthermore, treatment with quercetin ameliorated diabetes and related heart injury in rats, evidenced by the lowered blood glucose levels and notable inhibition of inflammatory markers and oxidative stress in the heart, supporting the cardioprotective effect of quercetin [149]. Clinically, delayed wound healing as a result of peripheral neuropathy presented a challenging issue in the clinical management of diabetic patients. In rodent models of diabetes, treatment with quercetin promoted wound healing, partially by modulating the inflammatory response through enhancement of M1 to M2 macrophage transition [150,151]. These results suggested that the key benefit of quercetin lays in its modulating effect on systemic and/or local inflammation.

6. Conclusions and future perspectives

Remarkable advances have been made in the identification of a large array of phytochemicals with anti-diabetic properties and our understanding of the mechanisms underlying their therapeutic actions. Promisingly, a vast body of evidence from basic and preclinical studies has revealed pleiotropic benefits of various phytochemicals for the treatment of diabetes, including the alleviation of hyperglycemia, hyperinsulinemia and insulin resistance, and prevention of complications (Fig. 4). Mounting evidence reveals multiple targeted events that correspond to the therapeutic potential of phytochemicals in diabetes, including metabolic inflammation, oxidative stress, insulin resistance, and altered gut microbiota. The hallmark of these bioactive phytochemicals and their therapeutic potential lies principally in their anti-inflammatory properties.

The crucial pathophysiology is known to be the key to development of new therapies for diabetes. Metabolic inflammation is well established as a crucial feature of diabetes, and evident in the pancreas, liver, adipose tissue, muscle, and other organs actively involved in metabolism. Furthermore, metabolic inflammation is profoundly modulated by various mediators of innate and adaptive immunity, making inflammation as the nexus within the crosstalk among key events in the pathogenesis of diabetes, including glucotoxicity, lipotoxicity, oxidative stress, endoplasmic reticulum stress, altered composition of gut microbiota, and dysfunction of the intestinal mucosal barrier

[49,50,152, 153]. Consequently, sustained metabolic inflammation is a potent driving force that promotes development of diabetes and progression of macrovascular and microvascular complications. The key role of metabolic inflammation may underlie the development of novel drugs for diabetes. Preclinical studies have demonstrated the anti-diabetic benefits of novel approaches that target mediators of inflammation, including IL-1 β , TNF- α , and IL-6, in the treatment of diabetes [17,23,28]. These advances suggest that phytochemicals and their anti-inflammatory properties hold great promise for diabetes treatment.

The pleiotropic benefits of a large array of phytochemicals may be the holy grail that facilitates development of new anti-diabetic agents. First, use of newly characterized key pathophysiological mediators in the regulation of glucose homeostasis and metabolic immunity represents a suitable strategy to identify novel

of new anti-diabetic phytochemicals and extend our knowledge of the mechanisms that underlie their functions. Exploration of a combined use of phytochemicals with existing drug therapies is a promising means by which to achieve enhanced suppression of blood glucose levels, achieve long-term sustainability, and reduce pharmacotherapy and thus side effects. In T2DM patients prescribed metformin, glycemic control declines over time. Combination therapy is therefore an essential approach for optimal management of such patients. Well-designed preclinical and proof-of-principle clinical studies are essential to accelerate pharmacological progression to new phytochemical-based agents for diabetes. There is often a significant delay in transfer of findings and benefits of animal studies to humans. This is principally due to the poor quality of preclinical and proof-of-principle clinical studies. Further investigation of the new properties of existing phytochemicals and novel ones that target inflammatory pathways is

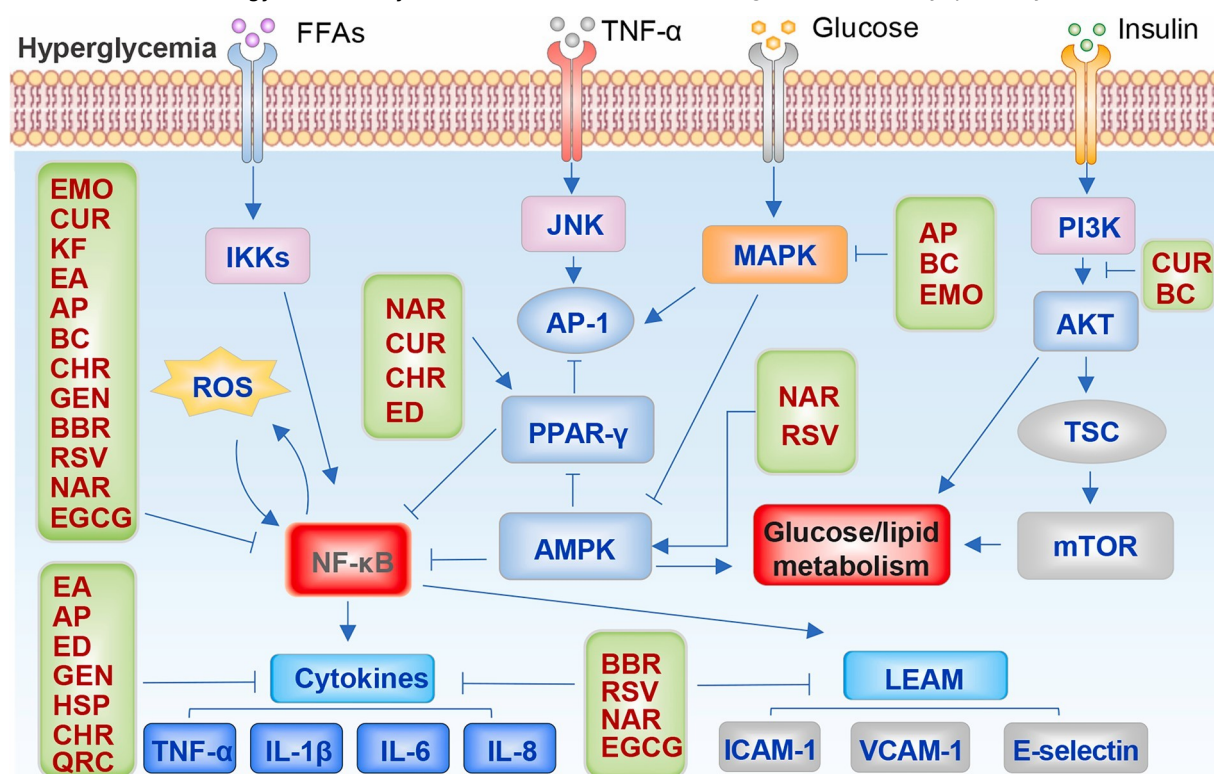


Fig. 4. Inflammatory signals act as the key targets that underlie the beneficial effects of phytochemicals in the management of diabetes and its complications. Metabolic inflammation plays a crucial role in the pathogenesis of diabetes and its complications (such as diabetic nephropathy, retinopathy and neuropathy). It is characterized by systemic inflammation as a result of sustained elevation of circulating levels of proinflammatory cytokines (IL-6, IL-1 β , TNF- α), chemokine-evoked enhanced recruitment of inflammatory cells in metabolic tissues, and activation of the inflammatory response consequent to the activation of NF- κ B and the signaling of AMPK and PPAR- γ . The beneficial effects of emerging anti-diabetic phytochemicals in the form of alkaloids, non-flavonoid polyphenols and flavonoid polyphenols function as the primary targets corresponding to essential modulators of inflammatory signals.

(Abbreviations. BBR, Berberine; RSV, Resveratrol; EMO, Emodin; EA, Ellagic acid; EGCG, Epigallocatechin gallate; CUR, Curcumin; BC, Baicalein; NAR, Naringenin; HSP, Hesperetin; CHR, Chrysin; GEN, Genistein; KPF, Kaempferol; ED, Eriodictyol; AP, Apigenin; QRC, Quercetin).

phytochemicals with anti-diabetic properties. The novel potential targets, such as α 1-antitrypsin, TNF- α , IL-6, IL-1 β , IL-37, glucokinase, glycogen phosphorylase, glucagon receptor, fructose 1,6-bisphosphatase, PTP-1B, have significantly contributed to the development of new candidate compounds for diabetes treatment [154,155]. The use of these promising targets in the context of high throughput screening may aid in the discovery

likely to be fruitful in the search for new drugs for type 2 diabetes.

Although a vast array of phytochemicals derived from medicinal plants or herbs exhibited notable anti-diabetic properties *in vitro*, most of them fail to exert sufficient biological activities *in vivo*, largely due to the insufficient absorption, reduced bioavailability, and the poorly characterized effective dose under *in vivo* conditions [156]. First,

the structure of chemical compounds is hydrolyzed and modified by various enzymes after they are administrated. This process may affect the biological properties of phytochemicals, including the bioavailability, anti-diabetic activity, specific interactions with cell receptors and enzymes. Thus, enzyme-mediated structure modifications should be taken into account during the development of phytochemical-based anti-diabetic drugs [157]. Second, hydrophobic or hydrophilic interactions between polyphenols and proteins may result in the formation of soluble or insoluble complexes, which can affect the bioavailability and anti-diabetic properties of polyphenols during the absorption, distribution, biotransformation and elimination under *in vivo* conditions [158]. Third, the bioavailability of dietary polyphenols is profoundly influenced by their degree of polymerization, in which gut microbiota plays a key role through modulating the production, bioavailability and the biological activities of phenolic metabolites [159]. Currently, the implementation of emerging novel strategies, including the novel technologies to uncover polyphenol-protein interactions and multi-omics approaches to characterize the pleiotropic roles of gut microbiota in modulating biological effects of phytochemicals, holds big promise to close the gap between *in vitro* and *in vivo* data regarding anti-diabetic effects of phytochemicals [160].

It is hoped that this updated and critical appraisal of the therapeutic promise of various phytochemicals in the treatment of diabetes, especially their anti-inflammatory properties, will encourage researchers to further explore novel anti-diabetic phytochemicals.

Ethical standards

This article does not contain any studies with human or animal subjects performed by any of the authors.

Declaration of Competing Interest

The authors have no conflicts to declare.

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